REMARKS/ARGUMENTS

I. AMENDMENTS

Upon entry of this amendment, claims 1, 4, 16-23 and 24-30 will be pending in this application and are presented for examination. Claims 2, 3, and 5-15 have been canceled without prejudice to future prosecution. Claims 1, 4, 16, 18, 22, and 23 have been amended. Claims 24-30 are newly added. No new matter has been added.

Table 3 on page 51 of the instant specification has been amended to correct a typographical error in the description of the SNP 12 variant allele.

Support for the phrase "independent of small bowel involvement" in amended claims 1, 16, and 18 is found, for example, in claim 2 as originally filed.

Claim 4 has been amended to establish proper dependency from claim 1.

Claim 22 has been amended to correct a typographical error.

Claims 24-30 are newly added and correspond to claims 16-22.

Support for the description of SNP 13 as recited in amended claims 1 and 23 can be found in Figure 7 and from page 23, line 16 to page 24, line 2. To assist in correlating the sequence of the recited SNP, attached as Exhibit 1 is a copy of Table 3 marked with the SNP 13 variant allele. The variant position is boxed. Exhibit 2 contains the relevant pages of the printout of Genbank Accession No. AC007728 showing the position of SNP 13 as referenced in the specification on page 23, lines 28-31. The boxed sequence in Exhibit 2 corresponds to the boxed sequence shown in Figure 7 (Exhibit 3), and the position of SNP 13 is marked with an asterisk. Exhibit 3 is a marked copy of Figure 7 showing the position of SNP 13.

The specification teaches that the SNP 13 allele corresponds to an insertion of a "C" at position 121,139 of Genbank Accession No. AC007728 (page 23, lines 28-31). In Exhibit 1, the wild-type "1" allele is shown with the position of the insertion indicated by an arrow, and the variant "2" allele is indicated with a box. Note that the "2" allele referred to in the specification on page 23, lines 28-31 corresponds to the opposite strand than that shown in Table 3 (insertion indicated to be "G"). The orientation referred to in the specification as the insertion

of "C" in the "2" allele is written out below in Exhibit 1. Exhibit 3 shows the position of the SNP 13 allele on both strands (position 248 of SEQ ID NO:5; position 294 of SEQ ID NO:6).

Accordingly, no new matter has been introduced with the foregoing amendments. Reconsideration is respectfully requested.

II. REJECTION UNDER 35 U.S.C. § 112, FIRST PARAGRAPH

A. Written Description

Claims 1-23 were rejected under 35 U.S.C. § 112, first paragraph, as allegedly lacking sufficient written description. In this regard, the Examiner alleges that the specification only discloses SNP 13 as being a fibrostenosis-predisposing allele linked to the NOD2 gene. To the extent the rejection applies to the amended claims, Applicants respectfully traverse the rejection.

In an earnest effort to expedite prosecution and without acquiescing on the merits of the rejection, Applicants have amended claims 1 and 23 to require the determination of the presence or absence of the SNP 13 allele in the NOD2 gene for the diagnosis or prediction of susceptibility to the fibrostenosing subtype of Crohn's disease. As such, the amended claims are drawn to methods of diagnosing or predicting susceptibility to a clinical subtype of Crohn's disease characterized by fibrostenosing disease, as well as optimizing therapy for a patient having the fibrostenosing clinical subtype, through the determination of the presence or absence of the SNP 13 allele.

In view of the foregoing, Applicants respectfully request that this rejection be reconsidered and withdrawn.

B. Enablement

Claims 1-23 were rejected under 35 U.S.C. § 112, first paragraph, as allegedly lacking enablement. In this regard, the Examiner alleges that the SNP 13 demonstrated the greatest association with fibrostenosing disease. To the extent the rejection applies to the amended claims, Applicants respectfully traverse the rejection.

As noted above, in an earnest effort to expedite prosecution and without acquiescing on the merits of the rejection, Applicants have amended claims 1 and 23 to require

the determination of the presence or absence of the SNP 13 allele in the NOD2 gene for the diagnosis or prediction of susceptibility to the fibrostenosing subtype of Crohn's disease. As such, the amended claims are drawn to methods of diagnosing or predicting susceptibility to a clinical subtype of Crohn's disease characterized by fibrostenosing disease, as well as optimizing therapy for a patient having the fibrostenosing clinical subtype, through the determination of the presence or absence of the SNP 13 allele.

Accordingly, Applicants respectfully request that this rejection be reconsidered and withdrawn.

III. REJECTION UNDER 35 U.S.C. § 102

For a rejection of claims under § 102 to be properly founded, the Examiner must establish that a single prior art reference either expressly or inherently discloses each and every element of the claimed invention. *See, e.g., Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 231 USPQ 81 (Fed. Cir. 1986), *cert. denied*, 480 U.S. 947 (1987); and *Verdegaal Bros. V. Union Oil Co. Of California*, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987).

In *Scripps Clinic & Research Found. v. Genentech, Inc.*, 18 USPQ2d 1001 (Fed. Cir. 1991), the Federal Circuit held that:

> Invalidity for anticipation requires that all of the elements and limitations of the claim are found with a single prior art reference. . . . There must be no difference between the claimed invention and the reference disclosure, as viewed by a person of ordinary skill in the field of the invention. *Id.* at 1010.

Anticipation can be found, therefore, only when a cited reference discloses all of the elements, features, or limitations of the presently claimed invention.

A. Ahmad *et al.*

Claims 1, 3-8, and 13-20 were rejected under 35 U.S.C. § 102(a) as allegedly being anticipated by Ahmad *et al.* (*Gastroenterology*, 122:854-866 (2002)). To the extent the rejection applies to the amended claims, Applicants respectfully traverse the rejection.

In an earnest effort to expedite prosecution and without acquiescing on the merits of the rejection, Applicants have amended claim 1 to recite a method of diagnosing or predicting

susceptibility to a clinical subtype of Crohn's disease characterized by fibrostenosing disease *independent of small bowel involvement*. Applicants assert that Ahmad *et al.* does not anticipate the presently claimed methods because each and every element as set forth in the amended claims is not found in the reference. Accordingly, Applicants respectfully request that the Examiner withdraw the rejection under 35 U.S.C. § 102(a).

B. Abreu *et al.*

Claims 1, 3-8, and 16-20 were rejected under 35 U.S.C. § 102(a) as allegedly being anticipated by Abreu *et al.*, *Gastroenterology*, Volume 122, No. 4, Supplement, page A-29, 246 ("the Abreu *et al.* Vol. 122 reference"). Claims 1, 3-8, and 16-20 were also rejected under 35 U.S.C. § 102(a) as allegedly being anticipated by Abreu *et al.*, *Gastroenterology*, Volume 123, pages 679-688 (2002) ("the Abreu *et al.* Vol. 123 reference"). To the extent the rejection applies to the amended claims, Applicants respectfully traverse the rejection.

Applicants submit herewith a Petition under 37 CFR § 1.48(b) to remove Kazuhito Sugimura as an inventor of the subject application as his inventive contribution is no longer being claimed. As a result, the inventors of the presently claimed subject matter are Maria T. Abreu, Kent D. Taylor, Jerome I. Rotter, Huiying Yang, and Stephan R. Targan. Applicants respectfully request that the Examiner update the inventorship entity of the instant application.

In addition, Applicants submit herewith a copy of the Declaration of Dr. Kent Taylor under 37 C.F.R. § 1.132, originally filed in U.S. Application No. 10/356,736[1], which explicitly states that to the extent that any subject matter disclosed in either Abreu *et al.* reference is described and/or claimed, the work relates only to the inventive contribution of Drs. Abreu, Taylor, Rotter, Yang, and Targan, and not to the other listed co-authors of the reference. Dr. Taylor's Declaration clearly sets forth the true inventive entity of the presently claimed subject matter and identifies the authors on each Abreu *et al.* reference who are not inventors.

In view of the foregoing, Applicants respectfully request withdrawal of the rejection under 35 U.S.C. § 102(a).

[1] The current application is a 35 USC § 371 national phase application of U.S. Application No. 10/356,736.

C. Radlmayr *et al.*

Claims 1, 3-8, and 16-20 were rejected under 35 U.S.C. § 102(a) as allegedly being anticipated by Radlmayr *et al.* (*Gastroenterology*, 122:2091-2092 (2002)). To the extent the rejection applies to the amended claims, Applicants respectfully traverse the rejection.

As explained above, Applicants have amended claim 1 to recite a method of diagnosing or predicting susceptibility to a clinical subtype of Crohn's disease characterized by fibrostenosing disease *independent of small bowel involvement*. Applicants assert that Radlmayr *et al.* do not anticipate the presently claimed methods because each and every element as set forth in the amended claims is not found in the reference. As such, Applicants respectfully request that the Examiner withdraw the rejection under 35 U.S.C. § 102(a).

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 925-472-5000.

Respectfully submitted,

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Attachments
JS:jch
61501548 v1

EXHIBIT 1

Table 3
TAQMAN PROBES

Allele detected	Probe sequence	Seq ID NO
SNP5 wild type allele ("1")	6FAM-CATGGCTGGACCC-MGBNFQ	45
SNP5 variant allele ("2")	TET-CATGGCTGGATCC-MGBNFQ	46
SNP8 wild type allele ("1")	6FAM-TGCTCCGGCGCCA-MGBNFQ	47
SNP8 variant allele ("2")	TET-CTGCTCTGGCGCCA-MGBNFQ	48
SNP12 wild type allele ("1")	6FAM-CTCTGTTGCCCCAGAA-MGBNFQ	49
SNP12 ~~wild type~~ variant allele ("2")	TET-CTCTGTTGCGCCAGA-MGBNFQ	50
SNP13 wild type allele ("1")	TET-CTTTCAAGGGCCTGC-MGBNFQ GAAAGTTCCCGGACG	51
SNP13 variant allele ("2")	6FAM-CCTTTCAAGGGCCCT-MGBNFQ GGAAAGTTCCCCGGA	52
JW1 wild type allele	6FAM-AAGACTCGAGTGTCCT-MGBNFQ	53
JW1 variant	VIC-AGACTCAAGTGTCCTC-MGBNFQ	54

As shown in Table 4, each of three rare allelic variants of NOD2/CARD15 (a "2" allele at SNP 8, SNP 12, or SNP 13) was significantly more frequent in patients

EXHIBIT 2

1: AC007728. Reports Homo sapiens chro...[gi:14277249] Links

Comment Features Sequence

```
LOCUS       AC007728               168271 bp    DNA     linear   PRI 01-JUN-2001
DEFINITION  Homo sapiens chromosome 16 clone RP11-327F22, complete sequence.
ACCESSION   AC007728
VERSION     AC007728.4  GI:14277249
KEYWORDS    HTG.
SOURCE      Homo sapiens (human)
  ORGANISM  Homo sapiens
            Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi;
            Mammalia; Eutheria; Euarchontoglires; Primates; Haplorrhini;
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REFERENCE   1  (bases 1 to 168271)
  AUTHORS   DOE Joint Genome Institute.
  TITLE     Sequencing of Human Chromosome 16
  JOURNAL   Unpublished
REFERENCE   2  (bases 1 to 168271)
  AUTHORS   Bruce,D., Mundt,M., Doggett,N., Munk,C., Saunders,E., Robinson,D.,
            Jones,M., Buckingham,J., Chasteen,L., Thompson,S., Goodwin,L.,
            Bryant,J., Tesmer,J., Meincke,L., Longmire,J., White,S., Tatum,O.,
            Campbell,C., Fawcett,J., Maltbie,M., Bussod,M., Sutherland,R.,
            McMurry,K., Han,C. and Deaven,L.
  TITLE     Direct Submission
  JOURNAL   Submitted (05-JUN-1999) Center for Human Genome Studies, DOE Joint
            Genome Institute, Los Alamos National Laboratory, MS M888, Los
            Alamos, NM 87545, USA
REFERENCE   3  (bases 1 to 168271)
  AUTHORS   DOE Joint Genome Institute.
  TITLE     Direct Submission
  JOURNAL   Submitted (01-JUN-2001) Production Sequencing Facility, DOE Joint
            Genome Institute, 2800 Mitchell Drive, Walnut Creek, CA 94598, USA
COMMENT     On Jun 1, 2001 this sequence version replaced gi:9795562.
            -------Genome Center
            Center: Joint Genome Institute
            Center Code: JGI
            Web site: http://www.jgi.doe.gov
            -------.
            Sequence Quality Assessment:
             This entry has been annotated with sequence quality
             estimates computed by the Phrap assembly program.
             All manually edited bases have been reduced to quality zero.
             Quality levels above 40 are expected to have less than
             1 error in 10,000 bp.
             Base-by-base quality values are not generally visible from the
             GenBank flat file format but are available as part
             of this entry's ASN.1 file.
            ----------------------.
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     source          1..168271
                     /organism="Homo sapiens"
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120781 agatgcaatt tctaggaggg cgggagctga cttttctttt cattcttcaa ccacatcccc
120841 attcctacac tatctcatag agcagagaag ttgctgaata aatagtcaag gtttaaaaat
120901 gaaatcattg ctccctactt aaagaggtaa agacttcttt cttagacaga gaatcagatc
120961 cttcacatgc agaatcattc tcactgaatg tcagaatcag aagggatcct caaaattctg
121021 ccattcctct ctcccgtcac cccattttac agatagaaaa actgaggttc ggagagctaa
121081 aacaggcctg cccaggggcc ttaccagact tccaggatgg tgtcattcct ttcaagggcc  SNP 13
121141 tgcaggaggg cttctgcccc taggtaggtg atgcagttat tggacaacct ggaaaagaag
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121621 tccaccatcc atctccttgt ggcatgggtc ctgggccatt aagtcagcca ccagtccccc
121681 attacctccc cacactctgc ttgctgggaa gacccaccac tctctgcatg cctaaaacac
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122821 cttgagaact caacatcgac cattccatgg tcattcagca tttgaagcaa attggaaagg
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124321 tcattgcctg gcatccatgg gagtcaagtg gagtaaggct gtgacaagga gggaagacaa
124381 acctgccata tccacacctg gttgataatg ggcttggtat tcccaaaggc cgaccctcag
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EXHIBIT 3

FIGURE 7

SNP 13